REMARKS

Reconsideration of the present Application in view of the present Amendments and the following remarks is respectfully requested. Claims 35, 40, 42, 44, 46 and 47 are currently pending. Solely for purposes of advancing prosecution of this application, Applicants have cancelled claims 46 and 47 without acquiescence to any rejection and without prejudice to further prosecution of this subject matter in a related divisional, continuation, or continuation-in-part application. Applicants have amended claims 35 and 44 to define more clearly the subject matter that Applicants regard as their invention, and to place the claims in condition for allowance. Support for the amended claims may be found in the specification, for example, at page 19, line 29 through page 20, line 17, and at page 33, lines 10-16. No new subject matter has been added.

REJECTION UNDER 35 U.S.C. § 112, FIRST PARAGRAPH (ENABLEMENT)

The PTO rejects claims 35, 40, 42, 44, 46 and 47 under 35 U.S.C. § 112, first paragraph, for lack of enablement. The PTO concedes that the specification is enabling for a "transgenic Scurfy mouse whose somatic and germ cells express a transgene comprising a 30kb fragment of normal genomic DNA, including ~7kb coding region of *Fkh*^{sf} gene as well as ~20kb of upstream flanking sequence and ~4kb of down stream sequences that contain a sequence encoding mouse Fkh^{sf} protein wherein expression of exogenous *Fkh*^{sf} transgene results in reduction of T-lymphocyte proliferation in the scurfy mouse." The PTO alleges, however, that the specification does not enable a skilled artisan, without undue experimentation, to make and use a transgenic mouse whose cells express a murine or human *Fkh*^{sf} transgene (SEQ ID NO:1 or 3, respectively), wherein the expression of the *Fkh*^{sf} transgene results in reduction of T-lymphocyte proliferation in the mammal.

Applicants respectfully traverse this rejection and submit that as disclosed in the present specification and recited in the instant claims, Applicants fully enabled the claimed invention at the time the instant Application was filed. Applicants' invention is directed in pertinent part to a transgenic mouse whose cells express an *Fkh*^{sf} transgene comprising a nucleic acid molecule that comprises a nucleotide sequence encoding a polypeptide comprising the

amino acid sequence of SEQ ID NO:2 or SEQ ID NO:4, wherein the nucleotide sequence is operably linked to a promoter effective for the expression of the Fkh^{sf} polypeptide (mouse) or FKH^{sf} polypeptide (human), respectively, and wherein proliferation of T lymphocytes that are obtained from the transgenic mouse expressing the *Fkh*^{sf} transgene is reduced when compared to proliferation of T cells obtained from a scurfy mouse.

Applicants respectfully point out that the PTO has mischaracterized the nature of the present invention (*see* Action, page 3, first paragraph). The invention as claimed and described in the specification is *not* directed to a transgenic scurfy mouse but is instead directed to a transgenic mouse that is derived by microinjecting *normal* genomic DNA that contains the *wildtype* Fkh^{sf} or FKH^{sf} coding sequence into *normal* mouse one-cell embryos (*see* specification, page 33, lines 10-14). These animals do not express the mutant polypeptide that contains the sf mutation, a two base insertion in the *Fkh*^{sf} coding region (*see* page 32, lines 20-25), but express excess normal, wildtype Fkh^{sf} polypeptide (*see* page 37, lines 15-17).

Applicants respectfully submit that, contrary to the assertion by the PTO, the *Fkh*^{sf} transgene used to make the claimed transgenic mice is described in the specification by structure and function. Moreover, in view of the state of the art with respect to making transgenic mice and in view of enabling guidance provided in working examples that describe making the subject invention transgenic mouse, the specification teaches a skilled artisan how to make and use the claimed transgenic mice. As taught in the specification, wildtype *Fkh*^{sf} gene products include murine Fkh^{sf} polypeptide (SEQ ID NO:2) and its human homologue FKH^{sf} polypeptide (SEQ ID NO:4). Transgenic mice whose cells express an *Fkh*^{sf} transgene encoding a wildtype gene product can be made by injecting pronuclei of normal mouse one-cell embryos with genomic DNA that contains the *Fkh*^{sf} gene and which is operably linked to a promoter that is effective for expression of the gene according to methods described in the specification and known in the art (*see, e.g.,* page 19, line 29 through page 20, line 17; Example 1, page 33, lines 10-14). Also as described in the specification and known in the art, tissue-specific expression of a transgene may be achieved by using a tissue-specific promoter, or alternatively, expression of the transgene may be regulated by using an inducible promoter (*e.g.,* page 20, lines 14-17).

The nucleotide sequences that encode the wildtype *Fkh*^{sf} gene products (SEQ ID NO:1 (mouse) and SEQ ID NO:3 (human)) are taught in the specification. These sequences may be used for isolating the portion of the genome that encodes these gene products according to methods described in the specification and well known in the art (*see, e.g.,* page 10, lines 12-25; page 32, line 5 through page 33, line 7). The specification further teaches in a working example that a fragment of the mouse genome so identified, which also comprises upstream and downstream nucleotide sequences that contain appropriately positioned expression control sequences, may be used to generate the claimed transgenic mice (*e.g.,* page 33, lines 10-27; *see also* page 20, lines 9-11). Integration of the injected DNA can be detected by methods known in the art, such as dot blot analysis of DNA from tissue samples (*see, e.g.,* page 20, lines 9-14; page 33, lines 14-16). While generating transgenic mice may be laborious, the instant specification provides enabling guidance in working examples for a skilled artisan to make the claimed transgenic mice (*see In re Wands*, 858 F.2d 731, 737 (Fed. Cir. 1988) (The test for undue experimentation is not merely quantitative because a considerable amount of routine experimentation is permissible when guidance is provided with respect to the direction in which the experimentation should proceed.)).

The specification also teaches a skilled artisan how to determine whether the transgene has been successfully incorporated into the genome of the mouse by evaluating immune function of the transgenic animal. As described in the specification and recited in the instant claims, T cells from such transgenic mice have a diminished capacity to respond to stimuli; thus, proliferation of T lymphocytes obtained from the transgenic mouse expressing the *Fkh*^{sf} transgene is reduced when compared to proliferation of T cells obtained from a scurfy mouse (*see, e.g.,* page 37, line 28 through page 38, line 5; Figure 8). As provided in the working example, in the presence of T lymphocyte stimulation, such as reacting the cells with antibodies that bind to CD3 and CD28 cell surface receptors, responsiveness of T cells from the transgenic mice is reduced compared to the responsiveness of T cells from normal animals and from scurfy mice (*see, e.g., id.*). These transgenic mice also have a reduced number of lymphoid cells in their lymph nodes (*see, e.g.,* page 37, lines 22-23; Figure 7). Thus, the instant specification provides enabling guidance to a skilled artisan to assess, readily and without undue

experimentation, parameters related to the immune competence of the subject invention transgenic mice that express the *Fkh*^{sf} transgene (*see, e.g.,* page 37, line 15 through page 38, line 5).

Applicants respectfully disagree with the assertion in the Action that low transgenic efficiency in farm animals and in lab animals renders the present invention so unpredictable that a skilled artisan is not enabled to make and use the claimed transgenic mice. For reasons already made of record, the instant specification, which includes working examples, enables the claimed invention even if some experimentation is required. *See In re Vaeck*, 947 F.2d 488, 495, 20 U.S.P.Q.2d 1438 (Fed. Cir. 1991) ("That some experimentation is required is not fatal" to showing that the specification enables the claimed invention.). Furthermore, in *In re Wands,* a success rate of 2.8% was not considered by the court to necessitate a finding of undue experimentation.

> Even if we were to accept the PTO's 2.8% success rate, we would not be required to reach a conclusion of undue experimentation. Such a determination must be made in view of the circumstances of each case and cannot be made solely by reference to a particular numerical cutoff.
> (*In re Wands,* 858 F.2d at 740, n.29)

See also Ex parte Chen, 61 U.S.P.Q. 2d 1025, 1028 (Bd. Pat. App. & Interfer. 2000) (finding that even though a success rate for an experimental procedure making a transgenic carp was 1%, the amount of experimentation was not undue). Therefore, reliance by the PTO on the "low" range of transgene efficiency (1-3%) cannot lead to a conclusion of undue experimentation, particularly in a field of art in which the level of skill of the artisans is quite high.

Applicants submit that, contrary to the assertion by the PTO, the present specification enables making and using transgenic mice that express the human FKH^{sf} polypeptide. The two structural motifs that are present in the FKH^{sf} polypeptide are the single zinc finger domain (amino acids at positions 199-222 of SEQ ID NO:4, page 39, line 21 through page 40, line 14; *see also* Figure 4) and the forkhead, or winged-helix, domain at the extreme carboxy-terminus of the polypeptide (amino acids at positions 337-431 of SEQ ID NO:4, page

39, line 21 through page 40, line 14; *see also* Figure 4). As is well known in the art, such a forkhead domain is characteristic of transcription factors (*see, e.g.,* Shimeld, *FEBS Lett.* 410:124-25 (1997); Kaufmann et al., *Mech. Devel.* 57:3-20 (1996)). As is readily apparent to the skilled artisan given the instant disclosure, the degree of sequence identity shared by the mouse and human Fkh^{sf} forkhead domain amino acid sequences is high, approximately 96%. The percent amino acid sequence identity shared by the mouse and human Fkh^{sf} zinc finger domain sequences is also approximately 96%. Therefore, the similarity of structure between the mouse and human Fkh^{sf} polypeptides indicated by the overall shared amino acid identity (87%), and in particular by the high degree of sequence identity shared by the forkhead domains and zinc finger domains (96%) indicates that a transgenic mouse expressing the human FKH^{sf} polypeptide would have a similar state of immune competence as that observed in a transgenic mouse expressing the mouse Fkh^{sf} polypeptide.

Accordingly, Applicants respectfully submit that in view of the direction and guidance provided by the instant specification, which includes working examples, the present specification enables a skilled artisan to make and use the subject invention transgenic mice, readily and without undue experimentation. Applicants therefore submit that the present Application meets the requirements of 35 U.S.C. § 112, first paragraph and respectfully request that the rejection of the claims be withdrawn.

Applicants respectfully submit that all claims in the Application are allowable. Favorable consideration and a Notice of Allowance are earnestly solicited.

Respectfully submitted,

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Enclosed:

Third Supplemental IDS
PTO Form 1449 (1 pg.)
2 references

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